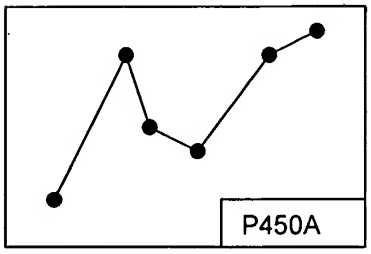
## REMARKS

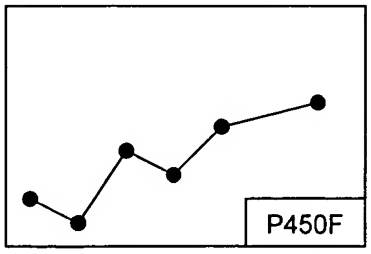
In the application, claims 2-4, 6-10, and 23-37 are pending and rejected. After due consideration of the Examiner's comments in the Office Action of December 5, 2005, the claims have been amended to more clearly set forth what Applicants regard as their invention. Applicants respectfully request reconsideration of the claims as amended.

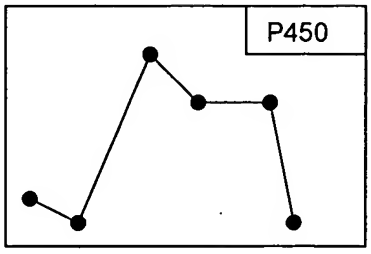
The Examiner has withdrawn all rejections from the Office Action of April 15, 2005, but has issued new rejections over the prior art, specifically, under 35 U.S.C. §103.

The Examiner rejects claims 2-4, 7-9, 24-28, 30, and 32 under 35 U.S.C. §103(a) as being unpatentable over Cunningham et al. in view of Hilsenbeck et al. in view of Johnston et al. While the amendments and arguments in Applicants' prior response had been successful in overcoming the rejection over the combination of Cunningham et al. and Hilsenbeck et al, the Examiner has added Johnston et al. for its reference to the step of varying dose.

The Examiner is of the opinion that Cunningham et al. teaches analysis of time variation on gene expression and, thus, meets the criteria for time stability specified in claims 2, 26 and 34. The Examiner specifically points to Table 1 of Cunningham, which plots gene expression over time. It is respectfully submitted that the Examiner fails to consider the *complete* definition of time stability that is stated in the specification, which is that the gene expression should progress in the same direction for two or more points and not change direction in adjacent time points relative to the time points where gene expression is changing. (See specification at page 29, lines 17-20). Patterns that meet these criteria are shown in Figure 1 of the application—there are no direction changes, i.e., negative to positive or positive to negative at adjacent points. In contrast, the data in Table 1 of Cunningham appear as follows when plotted. (Note that time scale is not accurate):



None of the plots show a recognizable pattern that conforms to the definition of "pattern" in the base claims. Thus, under the complete definition of time stability, the data points in Table 1 of Cunningham et al. do not meet these criteria since the gene expression values move up and down without any constancy, and change direction at adjacent points.

The foregoing amendments to the base claims (claims 2, 26 and 34) have added further clarification of the steps of the inventive method. In particular, the step of identifying patterns in the profiles/expression data that demonstrate time stability and dose dependence, where the pattern is defined where the change in expression (up- or down-regulation) is in the same direction with time and increased dosage and does not change direction at adjacent time points, has been included.

As previously stated, neither Cunningham et al. nor Hilsenbeck et al. teach or suggest using selection criteria in which gene expression data exhibits a particular pattern in response, where that pattern is both time and dose dependent and is consistent in the direction of change and does not change direction at adjacent time points. The Examiner has accepted this argument, but has added the Johnston, et al. reference for their disclosure of time and dose dependence.

The addition of Johnston, et al. to the combination of Cunningham et al. and Hisenbeck et al. provides the general concept of measurement of gene expression that is time stable and dose dependent, and admittedly, even one of the measured genes (Mt) displays a pattern of dose and time stability. However, Johnston et al. teach the application of statistical analysis to all data points, not only those that demonstrate a pattern of dose dependence and time stability, and that analysis was only to determine significance of observed variations at the different time points. There is nothing, apart from the present application, to teach or suggest the use of any statistical analysis to the data produced by Johnston et al.'s measurements that meet the claimed criteria for a pattern to create composite variables because there is only one such profile, and a composite cannot be generated from a single profile. The fact that one is able to measure gene expression, or even to measure gene expression that exhibits a pattern of dose dependence and time stability, would not motivate one in the art to select a plurality of profiles that meet

prescribed pattern criteria to generate composite variables and then to create a single predictive composite that comprises a binary value indicating one of a positive or negative toxicological response. Accordingly, it is respectfully submitted that the inventive method as now claimed is neither taught nor suggested by the combination of Cunningham et al, Hilsenbeck et al., and Johnston et al., and that the claimed invention is patentably distinct over the cited combination.

Claims 2 and 33 are rejected under 35 U.S.C. §103(a) as being unpatentable over Cunningham et al. in view of Hilsenbeck et al. in view of Johnston et al. and in further view of Holden et al. Holden et al. are relied on for their teaching regarding the measurement of carbon tetrachloride toxicity as detected by gene expression.

It is submitted that Holden et al. do not impart to the combination of Cunningham et al., Hilsenbeck et al. and Johnston et al. the missing subject matter needed to teach or suggest Applicants' invention. Specifically, Holden et al. do not teach or suggest selection of genes that fit patterns of time stability and dose dependence, creation of a set of composite variables, or the creation of one predictive composite that indicates toxicological response to the compound of interest. Accordingly the combination of the three references cannot render Applicants' invention obvious as now claimed.

The Examiner rejects claims 2, 10, 26, 28, 29 and 34-37 under 35 U.S.C. §103(a) as being unpatentable over Cunningham et al. in view of Hilsenbeck et al. in view of Johnston et al. and further in view of Machens et al. Machens et al. are relied on for their teaching of the use of logistic regression.

It is submitted that Machens et al. do not impart to the combination of Cunningham et al., Hilsenbeck et al., and Johnston et al. the missing subject matter needed to teach or suggest Applicants' invention. Specifically, Machens et al. do not teach or suggest selection of genes that fit patterns of time stability and dose dependence, creation of a set of composite variables, or the creation of one predictive composite that indicates toxicological response to the compound of interest. Accordingly, the combination of the three references does not render Applicants' invention obvious as now claimed.

The Examiner rejects claims 2, 23 and 37 under 35 U.S.C. §103(a) as being unpatentable over Cunningham et al. in view of Hilsenbeck et al. in view of Johnston et al. and further in view of Wikstrom et al. Wikstrom et al. is cited for its disclosure of the use of least squares analysis.

It is submitted that Wikstrom et al. do not impart to the combination of Cunningham et al., Hilsenbeck et al., and Johnston et al. the missing subject matter needed to teach or suggest Applicants' invention. Specifically, Wikstrom et al. do not teach or suggest selection of genes that fit patterns of time stability and dose dependence, creation of a set of composite variables, or the creation of one predictive composite that indicates toxicological response to the compound of interest. Accordingly the combination of the three references does not render Applicants' invention obvious as now claimed.

Applicants' invention as now claimed is addressed to a method for generating a predictive composite that is indicative of toxicological response to a compound of interest. The method combines three separate statistical analysis steps to achieve the desired goal. Each of the references relied on by the Examiner teaches no more than a single statistical step to classify data, and none suggests the use of even two distinct steps, much less three distinct steps to convert gene expression data into a predictive composite. As stated in the specification at page 31, beginning on line 9 (as amended):

> The classification of objects into one or more groups based on many measurements has several well established techniques. These include discriminate analysis, logistic regression, multidimensional scaling, clustering, and neural networks. ... All of these methods work by making composite measures from the many measurements taken from each object. With gene expression patterns we have several time and dose points which represent multiple objects that are grouped together. None of these techniques is sufficient alone to represent this order of complexity. Contrast analysis allows us to identify measurements that are partially independent of time because they are time stable yet are affected by toxic doses more then non-toxic doses. The PCA combines these many measurements into a series of orthogonal composite measures. Since these composite measures are non-correlated by definition the problem of multi-colinearity which can decrease the power of logistic regression is eliminated. By combining these techniques in the order described, many of the limitations of each individual technique is reduced.

Thus, an important advantage provided by the present invention is the reduction of limitations experienced with individual statistical techniques that are widely used in the prior art, including those relied on by the Examiner. Applicants achieve this improvement by sequentially combining the steps of multi-variate analysis, factor analysis and logistic regression to produce one predictive value of toxicity. None of the cited references teach or suggest such a method.

In view of the foregoing Amendment and remarks, Applicants submit that all bases for rejection have been addressed and overcome such that the claims are allowable over the prior art. Accordingly, Applicants respectfully request that the Examiner withdraw all rejections set forth in the Office Action and issue a notice of allowance for all claims in the application.

Should the Examiner believe that the prosecution of this application might be expedited by further discussion of the issues, he is invited to telephone the undersigned attorney for Applicant at the telephone number indicated below.

Respectfully submitted,

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By: _____

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